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Indirect spectrophotometric methods for the determination of Tadalafil

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ABSTRACT

Two spectrophotometric methods were developed for the determination Tadalafil in pharmaceutical preparations. The methods are based on the oxidation reaction with known excess amount of Ce(IV) and estimation of the unreacted amount using Indigo carmine dye (Method A) and in Methylene blue dye (Method B). the factors affecting the reaction conditions were studied and the absorbance of absorbance of the oxidation reaction products were monitored at 610 and 600 nm for methods A and B respectively. Beer's law is obeyed in the concentration ranges 11–50 and 10–55 ppm, the limits of detection and quantification are reported. The proposed method was applied to the determination of the drug in pharmaceutical formulations and the results demonstrated that the method is equally accurate, precise and reproducible as the official methods. The validity of method was established by recovery studies with satisfactory results.

Key words — Tadalafil, Spectrophotometry, Ce(IV), pharmaceutical

1. INTRODUCTION

Tadalafil (TDF) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), used in the management of erectile dysfunction. Chemically tadalafil is pyrazino- [1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol- 5-yl) 2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR) (Figure 1). It is not official in any of the pharmacopoeias. It is listed in the Merck Index [1] and Martindale, The Complete Drug Reference. Extensive literature survey revealed that the determination of TDF in pure and dosage forms are [2] not official in any pharmacopoeia and therefore, require much more investigation. Several analytical

methods that have been reported for the estimation of TDF in biological fluids or pharmaceutical dosage forms include liquid chromatography [3-7], densitometry [8] and spectrophotometry [9-11]. The well-established spectrophotometric method employs ion-pair extraction. In this case, an ion-pair is formed between basic compounds and an anionic dye such as bromocresol purple (BCP) and methyl orange (MO). At a specific pH, the ion-pair is extracted into an organic solvent, which is immiscible with water, and the concentration of the resulting ion pair in the organic phase is determined spectrophotometrically [12-20].

In the present investigation, we report the development of accurate, reproducible, less time consuming and adequately sensitive validated spectrophotometric methods for the determination of TDF based on its oxidation with excess amount of Ce(IV) in sulfuric acid, the residual amount of Ce(IV) bleaches Indigo carmine and Methylene blue dyes, then the residual amount of these dyes correlate with the amount of (TDF) in the original solution. Similar work was done by the author [21]. The proposed methods were applied to the determination of TDF in tablets dosage form. No interference was observed in the assay of TDF from common excipients in levels found in dosage form. These methods are validated by statistical data and can be adopted by the pharmaceutical laboratories for industrial quality control.

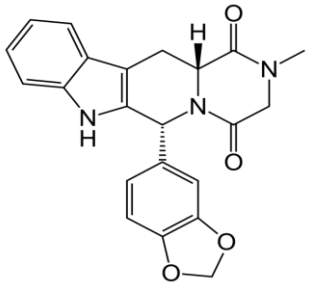

Figure 1 Chemical structure of Tadalafil

2. EXPERIMENTAL

A. Materials

A UV-Vis Double Beam (UVD- 3500, Labomed.Inco) was used with spectral bandwidth of 1.0 nm, wavelength accuracy ± 0.3 nm (with automatic wavelength correction), wavelength range (190 nm-1100 nm), wavelength reproducibility ± 0.2 nm and a pair of 1-cm matched quartz cells was used to measure absorbance of the resulting solution. All chemicals used were of analytical reagent grade and the solvents were spectroscopic grade. Double distilled water was used wherever required. Tadalafil tablets (Cialis), labeled to contain 20 mg Tadalafil per tablet. The stock solution of 220 ppm (TD) was prepared in acetonitrile solution and was used to prepare different standard solutions. An aqueous solutions of (IN) (Aldrich; 200 ppm) and (MB) (Merck; 100 ppm) and were prepared by dissolving the appropriate weight of the dye in a very small volume of water and then made up to 100 ml in a calibrated flask. The stock solutions of dyes were allowed to stand at room temperature for a few weeks without any significant decay. A stock solution of 100.0 ppm Ce(IV) (Aldrich) was prepared by dissolving the appropriate weight in 0.5 M H_2SO_4 solution. This solution was then standardized using sodium oxalate and stored in a dark.

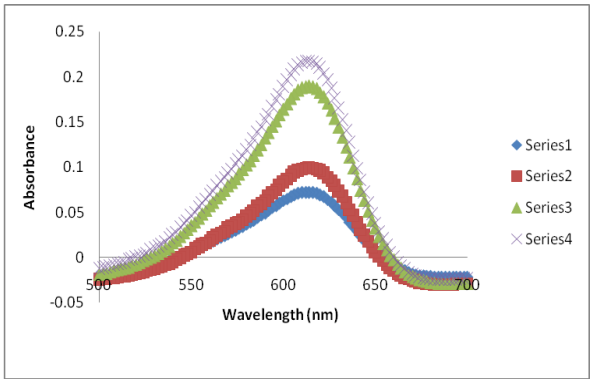

Figure 2 Effect of TD concentration on absorption spectrum using Method A.

B. Construction of calibration curves

Method A: Different volumes of standard (TD) (250 ppm) Solutions were pipette into 10 ml volumetric flasks, then 0.5 ml of Ce(IV) (100.0 ppm) solution was added the mixture was then shacked and kept for 10 minutes, after that 2.5 ml of the (IN) (200 ppm) then the solution was made up to the 10.0 ml with distilled water. The absorbance was then measured at (610 nm) after 10 minutes.

Method B: The same method above was performed as in method A except 2.0 ml of (MB) (100 ppm) dye solutions were used, the absorbance of the final solutions were measured at (600 nm).

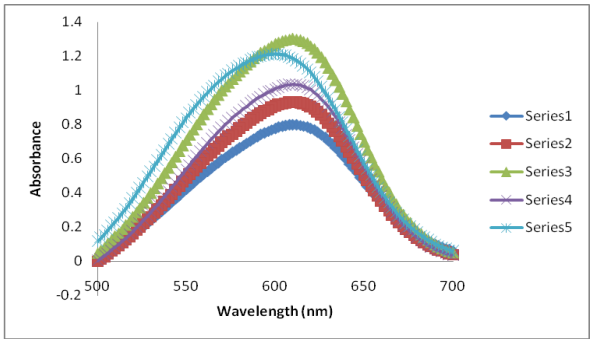

Figure 3 Effect of TD concentration on absorption spectrum using Method B.

C. Procedures for drug formulations

An amount of finely ground tablets equivalent to 2.0 mg of (TD) was accurately weighed, dissolved in appropriate amount of distilled water and transferred to a 100-ml volumetric flask, the

flask was sonicated for about 20 minutes, finally the volume was made up to the mark. The content was kept aside for 5 min, and filtered using 0.45µm GHP filter paper. The first 10-ml portion of the filtrate was discarded and a suitable aliquot was used for the assay as described under General analytical procedure for the proposed method or using HPLC method.

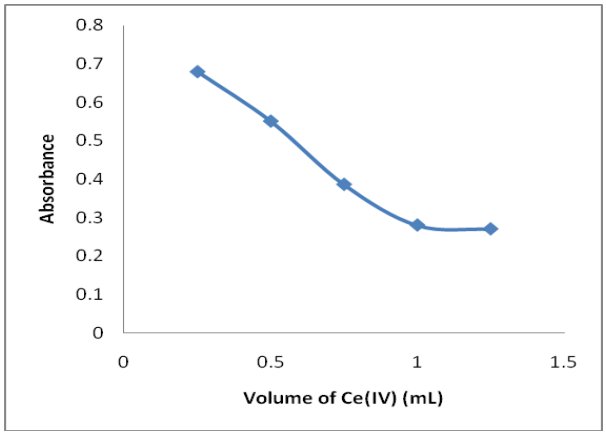

Figure 4 Effect of variation of volume of 1.0 mg/mL of Ce(IV) solutions on the Absorbance measured at 600 nm. (Method B).

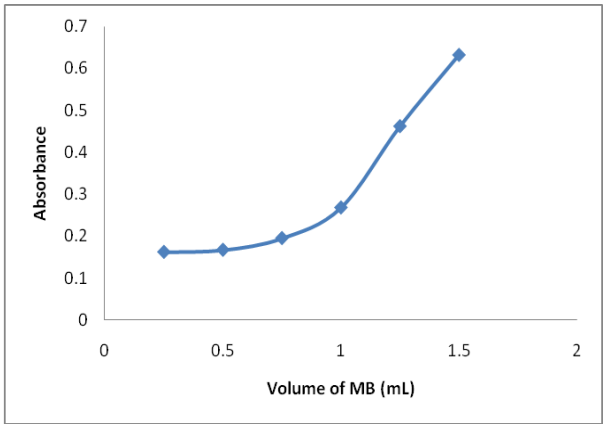

Figure 5 Effect of variation the volume of 100 µg/mL (MB) on Absorbance measured at 600 nm. (Method B).

3. RESULTS AND DISCUSSION

Tadalafil undergoes fast oxidation reaction with strong oxidizing agents. It is also shows no absorption band in the visible region which makes it difficult to be determined directly using simple spectrophotometric methods. So we suggest two simple and inexpensive procedures for the determination of (TD) in pure and pharmaceutical preparations based on treating (TD) solutions with an excess amount of oxidizing agent, then the residual amount of oxidant bleaches certain dye, so that the remaining amount of dye can be determined spectrophotometrically. As a result, a proportional increase in the absorbance for the two dyes is observed with increasing concentration of (TD).

In method A. Ce(IV) in sulfuric acid was used as oxidizing agent and (IN) was used as a dye the absorbance was measured at 610 nm.

In method B. Ce(IV) in sulfuric acid was used as oxidizing agent and (MB) was used as the dye which has a maximum absorption at 600 nm. Preliminary experiments were performed to fix the upper concentrations of the oxidants that could be used to maintain excess amounts. A Ce(IV) concentration of 8.0 ppm was found to bleach the color due to 5 ppm (IN) and (MB). For both methods the Absorbance was monitored at 25°C with time which showed that the oxidation reaction is fast and complete in five minutes, and contact times up to 8 minutes had no effect on the absorbance of dyes.

A. Optimum reaction conditions

The optimum conditions for color development in each method were established by varying the parameters one at a time, keeping the others fixed and observing the effect produced on the absorbance of the colored species for methods A and B. In a series of experiments, the volumes of both dyes were varied using the constant concentrations of both (TD) and the selected oxidants, the results which are shown in (Fig.2 & Fig.3) revealed that the optimum volumes of both Indigo carmine and Methylene Blue dyes were 2.5 and 2 ml of the given concentrations respectively. For Methods A and B the effect of time on the absorbance values were investigated, the obtained results show no appreciable change after eight minutes, so it decided to measure the absorbance after 10 minutes from preparing the mixtures as shown in (Fig. 4).

B. Method validation

Analytical parameters:

Calibration curves for (TD) determination using the proposed methods A and B were constructed by plotting absorbance *vs.* concentration using the optimized amounts of oxidants and dyes. The intercepts, slopes, and correlation coefficients were calculated using the method of least squares. Beer's law is obeyed over concentration ranges of 11-50 ppm for (Method A) and 10-55 ppm for (Method B). The mean molar absorptivity (ε), limit of detection (LOD = 3s/k) and limit of quantitation (LOQ = 10s/k) were calculated, where s is the standard deviation of replicate determinations in the absence of analyte under the same conditions as sample analysis and k is the slope. The LOD were 1.5 and 2.3 ppm using methods A and B respectively, these statistical results are shown in (Table 1) below.

Application to drug formulation:

The suggested method were applied successfully for the determination of Tadalafil in commercial tablets, Statistical comparison of the accuracy and precision of the proposed methods with an HPLC method was performed using Student's

t-tests at a 95% confidence level. The t-values did not exceed the theoretical values; there is no significant difference in accuracy or precision between the proposed and the official method as shown in (Table 2).

Table 1 Statistical analysis of calibration graphs and analytical data in the determination of Tadalafil

Parameters	Proposed methods	
	Method A	Method B
Wavelengths λ_{max} (nm)	610	660
Regression equation		
Slope (*b*)	0.0923	0.0319
Intercept (*a*)	0.0014	0.109
Correlation coefficient (*r*)	0.9967	0.9968
Beer's law limits (µg/ml)	11–50	10–55
Sandell, *s* sensitivity (ng/cm)	10.52	23.91
LOD (µg/ml)	3.5	2.3
LOQ (µg/ml)	11.66	7.59
R.S.D.%	0.773	1.3655
Molar absorptivity ε, (l mol^{-1} cm^{-1})[a]	811.9	836.7

Table 2 Comparison between the proposed method and the standard method

Proposed method		Standard method		
Amount taken (µg/ml)	Recovery ± RSD%	Amount taken (µg/ml)	Recovery ± RSD%	t-value
Method A 20	97% ± 8	20	98% ±2	0.85
Method B 20	98% ± 8	20	97% ±2	0.56

Tabulated student t-value at 95% confidence level and 6 degrees of freedom. (2.44)

4. CONCLUSION

Tadalafil was determined in a two simple spectrophotometric methods that based on oxidation the drug by Ce(IV) oxidant in the presence of Indigo.

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